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PERCUTANEOUS-ABSORBABLE PHARMACEUTICAL AND METHOD FOR PERCUTANEOUS ADMINISTRATION
[Keihi kyushu seizai oyobi keihi toyoho]

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Specifications /137*

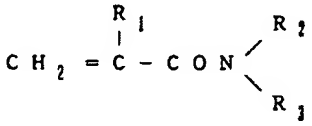
1. Title of the Invention

PERCUTANEOUS-ABSORBABLE PHARMACEUTICAL AND METHOD FOR PERCUTANEOUS ADMINISTRATION

2. Claim(s)

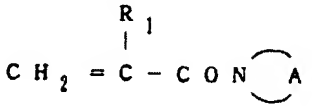
(1) A percutaneous-absorbable pharmaceutical characterized by using a temperature-responsive hydrogel membrane for a release control membrane.

(2) The percutaneous-absorbable pharmaceutical of Claim 1 characterized by the aforesaid temperature-responsive hydrogel membrane being a water-insoluble polymer obtained by using a compound shown by formula (I) and/or a compound shown by formula (II):



(I)

(R_1 denotes a hydrogen atom or a methyl group; and R_2 and R_3 denote hydrogen atoms and lower alkyl groups where R_2 and R_3 may be the same or different, but at one of these denotes a lower alkyl group.)



(II)

(R_1 in the formula denotes a hydrogen atom or methyl group and **A** denotes $+CH_2+_n$ where **n** is 4 to 6, or $+CH_2+_2O+CH_2+_2$).

(3) A method for percutaneous administration characterized by administering a drug on or off according to a temperature change and using the percutaneous-absorbable pharmaceutical of Claim 1 or 2 to deliver

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* Number in the margin indicates pagination in the foreign text.

said pharmaceutical into the circulatory system through the skin at a steady state flow rate in the "on" administration period and at a smaller steady state flow rate or a substantially zero flow rate in the "off" administration period.

3. Detailed Specifications

[Field of Industrial Application)

The present invention relates to a method for percutaneous administration and a percutaneous-absorbable pharmaceutical used in this method, and in particular, is characterized by using a temperature- /138 responsive hydrogel membrane which reversibly changes in form with respect to a change in temperature to control the permeation or release of a drug according to the temperature, delivering the drug to the circulatory system percutaneously in the required period when the drug is necessary, and pausing the percutaneous administration in a period when no drug is required.

[Prior Art]

Methods for delivering drugs to the blood circulating system at a steady state flow rate through the skin are already conventionally known.

For example, an overview of percutaneous administration drug products that are currently commercially-available is disclosed in the reference "Percutaneous-absorbable Pharmaceuticals and Their Mechanisms" Pharmacy Vol. 39, Issue 9, pp. 1293-1300 (1988). As show here, various types of percutaneous-absorbable pharmaceuticals are commercially-available capable of delivering drugs into the circulatory system for 24 hours or longer at a steady-state flow rate. For example, Transderm-Nitro® (made by Alisa Systems and Ciba-Geigy) comprises four 4 layers: a covering membrane,

drug storing layer, release-control membrane and a tacky layer. Release of nitroglycerin in the drug storing layer is controlled by the release-control membrane at a steady-state flow rate. The average nitroglycerin concentration in plasma when two pieces of this Transderm-Nitro® are adhered to the left pectoral region is maintained constantly at 200 to 300 ps/mL for 24 hours.

[Problems to be Solved by the Invention]

The basic limits of these percutaneous-absorbable pharmaceuticals are designed for the purpose of only supplying drugs into the circulatory system at a steady flow rate during the administration period. That is, side effects are sometimes expressed due to long-term sustained administration of drugs at a steady flow rate.

For example, as described in "How to Use Percutaneous-absorbable Nitrate Drugs—Expression of Resistance and Countermeasures Thereof" Pharmacia Vol. 24, Issue 7, pp. 699-702(1988), a problem is observed because resistance is expressed in long-term administration of nitroglycerin.

[Means for Solving the Problems]

In order to solve the above-mentioned problem, it is desirable construct an administration program so that the administration period in which the concentration of the drug in the blood expressing action is maintained for any given length of time ("on" administration period) and the administration period in which the concentration of the drug in the blood persistently disappears for any given length of time ("off" administration period) are recycled.

As a result of painstaking research in order to solve the above-mentioned problems, the inventors of the present invention discovered that such an administration program could be achieved by using a temperature-responsive hydrogel membrane.

That is, the inventors of the present invention noticed that a hydrogel, which was a water-insoluble polymer obtained by using, e.g., a compound shown by the formula (I) given below and/or the compound shown by the formula (II) given below as the active ingredient had a phase transition temperature, and conversely thereto, that the morphology changed by changing the temperature, that is, it had "temperature-responsiveness." As a result of painstaking studies of the use of these hydrogels as membranes for controlling the administration of drugs to be on or off, the inventors of the present invention proved that drug passage could be controlled at or higher than the phase transition temperature and the behavior thereof did not vary from repeated changes in temperature.

The present invention was accomplished on the basis of such findings.

That is, the present invention relates to (1) a percutaneous-absorbable pharmaceutical characterized by using a temperature-responsive hydrogel membrane for a release control membrane and (2) a method for percutaneous administration characterized by administering a drug on or off according to a temperature change and using the percutaneous-absorbable pharmaceutical of claim 1 or 2 to deliver said pharmaceutical into the circulatory system through the skin at a steady state flow rate in the "on" administration period and at a smaller steady state flow rate or a substantially /139 zero flow rate in the "off" administration period.

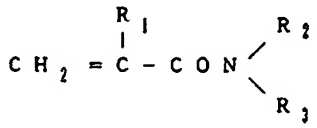
In the present invention, "temperature-responsive hydrogel membrane" refers to a membrane able to swell by absorbing water at or below the phase transition temperature and contract by releasing water at or above the phase transition temperature. This swelling and contracting behavior occurs reversibly in the presence of water. Furthermore, this reversible change is surface rate-limiting; hence, a rapid change can be performed.

The percutaneous-absorbable pharmaceutical of the present invention may be any of various types known in the past, such as those described in the aforesaid references. The temperature-responsive hydrogel membrane should be used as a release control membrane. (Even with different descriptions, the membrane wholly includes a membrane which is interposed between the layer where the drug is stored substantially and this drug passes through the membrane thereof to the skin.)

The percutaneous-absorbable pharmaceutical in the present invention normally comprises four types of configurations including a covering membrane, drug storing layer, temperature-responsive hydrogel membrane and a tacky layer. The covering membrane may be a membrane as long as it furnishes impermeability to the drug or the contents in the drug storing layer. An aluminum foil or the like is cited as an example thereof. The drug should be an aqueous or a water-based drug which can be maintained for a prescribed amount of time at a saturated concentration. For example, a drug at or above the saturated concentration is desirably a liquid or gel-like one in which a carrier having the drug at or above the saturated concentration has been dispersed in a water-based solvent. For example, the below-mentioned hydrogel membranes can be used for the

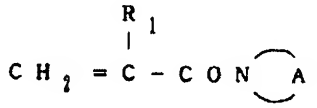
temperature-responsive hydrogel membrane. The tacky layer is used for adhering the hydrogel membrane to the skin. A silicone-based pressure-sensitive adhesive that hardly irritates the skin can be cited as an example therefor.

A water-insoluble polymer obtained using a compound shown by formula (I) and/or a compound shown by formula (II):



(I)

(R_1 denotes a hydrogen atom or a methyl group; and R_2 and R_3 denote hydrogen atoms and lower alkyl groups, and preferably, R_2 is a hydrogen atom, methyl group or ethyl group and R_3 is a methyl group, ethyl group or propyl group, where R_2 and R_3 may be the same or different, but at one of these denotes a lower alkyl group.)



(II)

(R_1 in the formula denotes a hydrogen atom or methyl group and **A** denotes $+CH_2+_n$ where **n** is 4 to 6, or $+CH_2+_2O+CH_2+_2$) can be cited as a typical example of this temperature-responsive hydrogel membrane.

Such a polymer is one having the compound shown by the above-mentioned formula (I) and/or the compound shown by the formula (II) or a copolymer having these compounds and other monomers copolymerizable with these compounds, and is insoluble in water.

N-n-propylacrylamide, N-n-propylmethacrylamide, N-isopropylacrylamide, N-isopropylmethacrylamide, N-ethylacrylamide,

N,N-diethylacrylamide, N-ethylmethacrylamide, N,N-dimethylacrylamide, N,N-dimethylmethacrylamide, N-acryloylpyrrolidine, N-methacryloylpyrrolidine, N-acryloylpiperidine, N-methacryloylpiperidine, N-acryloylmorpholine, and the like can be cited specifically for the compound shown by the formula (I) or formula (II). /140

Moreover, a hydrophilic monomer, hydrophobic monomer, and the like can be cited for the monomer copolymerizable with the above-mentioned monomer, and one or more of these monomers may be used therefor. Acrylamides; methacrylamides; N-methylacrylamides; diacetonacrylamides; hydroxyethylmethacrylates; hydroxyethylacrylates; hydroxypropylmethacrylates; hydroxypropylacrylates; various methoxypolyethylene glycol methacrylates; various methoxypolyethylene glycol acrylates, N-vinyl-2-pyrrolidone; acids, such as acrylic acid, methacrylic acid, vinylsulfonic acid, allyl sulfonic acid, methacrylsulfonic acid, styrene sulfonic acid, 2-acrylamide-2-phenylpropane sulfonic acid and 2-acrylamide-2-methyl-propane sulfonic acid, and their salts; amines, their salts, and the like, such as N,N-dimethylaminoethylmethacrylate, N,N-diethylaminoethylmethacrylate, N,N-dimethylaminoethylacrylate, N,N-dimethylaminopropylmethacrylamide and N,N-dimethylaminopropylmethacrylamide; various acrylates, methacrylates, acrylamides, methacrylamides, acrylonitriles, vinyl acetates, glycidylmethacrylate, and the like are cited as specific examples of hydrophilic monomers. N-alkyl(meth)acrylamide derivatives; such as

N-n-butylacrylamide, N-n-butylmethacrylamide, N-tert-butylacrylamide, N-tert-butylmethacrylamide, N-n-hexylacrylamide, N-n-hexylmethacrylamide, N-n-octylacrylamide, N-n-octylmethacrylamide, N-tert-octylacrylamide, N-n-dodecylacrylamide and N-n-dodecylmethacrylamide; N(-ω-glycidoxyalkyl)(meth)acrylamide derivatives, such as N,N-diglycidylacrylamide, N,N-diglycidylmethacrylamide, N-(4-glycidoxybutyl)acrylamide, N-(4-glycidoxybutyl)methacrylamide, N-(5-glycidoxypentyl)acrylamide and N-(6-glycidoxyhexyl)acrylamide; (meth)acrylate derivatives, such as ethyl acrylate, methyl methacrylate, butyl methacrylate, butyl acrylate, lauryl acrylate, 2-ethylhexyl methacrylate and glycidyl methacrylate; acrylonitriles; methacrylonitriles; vinyl acetates; vinyl chlorides; olefins, such as ethylene, propylene and butene; styrene; α-methylstyrene; butadiene; isoprene; and the like can be cited as examples of hydrophobic monomers.

The method for obtaining the water-insoluble monomer of the polymer having the above-mentioned monomers includes insolubilizing methods during polymerization and insolubilizing methods in treatments after polymerization. A method for copolymerization with a crosslinkable monomer having two or more double bonds in the molecule (1st method), a method for copolymerization with N-alkoxymethyl(meth)acrylamide derivative (2nd method), a method for reacting a polyfunctional compound, such as epichlorohydrin, with the above and crosslinking them (3rd method), and the like may be cited specifically. The method may be any method as long as the polymer obtained finally is insoluble in water. /141

More specifically, N,N'-methylene bisacrylamide, N,N'-diallylacrylamide, triacrylformal, N,N'-diacryloylimide, N,N'-dimethacryloylimide, ethylene glycol diacrylate, ethylene glycol dimethacrylate, various polyethylene glycol diacrylates, various polyethylene glycol dimethacrylates, propylene glycol diacrylates, propylene glycol dimethacrylates, various propylene glycol diacrylates, various propylene glycol dimethacrylates, 1,3-butylene glycol diacrylate, 1,3-butylene glycol dimethacrylate, 1,4-butylene glycol dimethacrylate, glycerol dimethacrylate, neopentyl glycol dimethacrylate, trimethylol propane triacrylate, trimethylol propane trimethacrylate, trimethylol ethane trimethacrylate, trimethylol ethane triacrylate, tetramethylol methane tetramethacrylate, tetramethylol methane triacrylate, divinylbenzene diallylphthalate, and the like can be used for the crosslinkable monomer in the 1st method.

N-methylol(meth)acrylamide, N-methoxymethyl(meth)acrylamide, N-ethoxymethyl(meth)acrylamide, N-n-butoxymethyl(meth)acrylamide, N-tert-butoxymethyl(meth)acrylamide, and the like can be used as examples of the N-alkoxymethyl(meth)acrylamide in the 2nd method.

In the 3rd method, an amino group can be introduced easily by copolymerization, but a hydroxyl group is introduced by copolymerization with hydroxyethylmethacrylate or the like and vinyl acetate or the like is introduced by copolymerization, this is subsequently hydrolyzed, then this amino group or hydroxyl group is reacted with a polyfunctional compound, such as epichlorohydrin, in the presence of a basic substance to render it insoluble.

50 mol.% or more of the compound shown by formula (I) and/or the compound shown by the formula (II) is preferably used in the whole amount of the monomer thus polymerized, and in particular, 75 mol.% or more of it is used preferably.

A polymerization method in which the monomer is poured into a template as is without dilution with a solvent, a polymerization method in which the monomer is dissolved in a solvent and poured into a template, a polymerization method in which a monomer or a filmy substance in which the monomer is dissolved in a solvent is impregnated, a graft polymerization method, or the like is cited as a specific polymerization method for obtaining a gel membrane able to be used in the present invention in accordance with the above-mentioned method. In such case, a method for initiating polymerization is performed merely by heating, but normally, more satisfactory results are obtained when a polymerization initiator is used. As long as it has the ability to initialize a radical polymerization, the polymerization initiator is not restricted and examples of it include combinations of their peroxides and reducing agents, azo compounds, and the like, and specifically, ammonium persulfide, potassium persulfide, hydrogen peroxide, tert-butylperoxide, benzoyl peroxide, tert-butylperoxy-2-ethylhexanoate, butyl perbenzoate etc. Sulfites, hydrogen sulfites, iron, copper, cobalt, and the like salts, organoamines, such as aniline; and the like can be cited as reducing agents combined therewith. Azobisisobutyronitrile, 2,2'-azobis-2-aminidinopropane hydrochloride, 2,2'-azobis-2,4-dimethylvaleronitrile, and the like /142 can be used for the azo compound. The amount of these polymerization

initiators added is sufficient in a range adopted in the usual radical polymerization, such as a range of 0.01 to 5 wt.%, and preferably, 0.05 to 2 wt.% per monomer.

The gel membrane obtained by the above process is washed with a solvent in which unreacted matter cannot dissolve and has phase solubility with water, and subsequently substituted sufficiently with water to obtain a hydrogel membrane. The thickness of the hydrogel membrane used in the present invention preferably falls in a range of 0.01 to 1.0 mm, and more preferably, 0.05 to 0.5 mm. The amount of water contained in 1 g of hydrogel membrane at a concentration at or above the phase transition temperature is preferably 0.1 to 0.6 g.

Furthermore, the drug used in the present invention may be any drug as long as it permeates through the skin; nitroglycerin, isosorbide nitrate, nifedipine, salbutamol, and the like are cited as examples therefor.

When the percutaneous-absorbable pharmaceutical of the present invention is used, burning of the skin occurs if the temperature thus changed is too high, and if it is too low, frostbite of the skin occurs; hence, the phase transition temperature of the hydrogel membrane is at or below a temperature at which skin causes burning, and it is necessary that it be at or above a temperature that causes frostbite on the skin. That is, the phase transition temperature of the hydrogel membrane used in the present invention specifically falls in a range of 9 to 50°C, preferably, 10 to 37°C, and preferably, 28 to 32°C.

The phase transition temperature of the hydrogel membrane in the present invention can be changed freely, depending on the type of compound

shown by the formula (I) or formula (II), the type or composition ratio of the copolymerized monomers, and the type and composition ratio of the crosslinking agent. For example, the phase transition temperature of the hydrogel membrane in Practical Example 1 shown below is 26°C, and the phase transition temperature of the hydrogel membrane in Practical Example 2 is 23°C.

Furthermore, the permeability of the drug at a temperature which is at or below the phase transition temperature of the hydrogel membrane used in the present invention can be changed freely depending on the type of compound shown by the formula (I) or formula (II), the type or composition ratio of the copolymerized monomers, and the type and composition ratio of the crosslinking agent. For example, with the hydrogel membrane of Practical Example 1, the permeability coefficient of nitroglycerin at 22°C was 4.0×10^{-8} cm/sec, and with the hydrogel membrane of Practical Example 2, the permeability coefficient of nitroglycerin at 22°C was 3.1×10^{-8} cm/sec. Moreover, at the temperature at or above the phase transition temperature of these hydrogel membranes (32°C), the amount of permeated drug was substantially zero.

The permeation coefficient of the drug with respect to the skin varies depending on the type, age in weeks or years of the animal, the site, and the like; hence, a difference in the number of individuals occurs at the concentration of the drug in the blood, assuming the drug is delivered to the circulatory system through the skin from a membrane that does not do a certain specific control.

That is, assuming the permeation coefficient of the drug with respect to the membrane is P(membrane), and permeation coefficient of the drug type needing to be administrated with respect to the skin is P(skin), and assuming the net permeability coefficient released from the membrane through the skin is P(net), the next relational formula is established:

$$1/P(net)=1/P(skin)+1/P(membrane) \quad (1)$$

Hence, the concentration of the drug in the blood is related to the permeability coefficient of the skin if a membrane that does not do a certain specific control; hence, an individual difference occurs.

The "on" percutaneous administration period or the "off" percutaneous administration period is preferably designed by applying a specific control so as to satisfy the conditions below in order to decrease or eliminate the above-mentioned individual difference using the percutaneous-absorbable pharmaceutical of the present invention.

$$P(net)/P(skin)\times 100 \geq 50\% \quad (2)$$

That is, in order to obtain a membrane rate-limiting /143
percutaneous administration system to reduce the individual difference, it is desirable to set the conditions of expression (2) to 50 to 100%, and preferably, 70 to 90%.

The conditions of the expression (2) can be satisfied by suitably selecting the type of compound shown by the formula (I) or formula (II), the type or composition ratio of copolymerized monomers, and the type of composition ratio of the crosslinking agent.

In the present invention, upon attempting to turn a percutaneous administration of a drug on or off using the percutaneous-absorbable

pharmaceutical having the hydrogel membrane designed for each of the above-mentioned conditions, it was proven that in the "on" administration period, a certain fixed concentration of the drug in the blood is obtained, and that a small individual difference can be achieved by allowing the concentration of the drug in the blood to disappear in the "off" administration period.

The percutaneous-absorbable pharmaceutical of the present invention is used by adhering the percutaneous-absorbable pharmaceutical (e.g., one in which the covering membrane, drug storing layer, temperature-responsive hydrogel membrane and tacky layer are provided in that order) to the skin upon bringing the tacky layer in contact with the skin. The administration of the drug on and off can be performed by using, e.g., a cooling device or the like, depending on the change in temperature to control the temperature from the outside in the required time.

(Advantages of the Invention)

According to the percutaneous-absorbable pharmaceutical of the present invention and the method for using it, the percutaneous administration of the drug can be controlled to on or off with little individual difference in response to changes in the external temperature, it can be used in pharmaceuticals for automated drug administration periods, and in intelligent pharmaceuticals responding to external stimuli.

[Practical Examples]

The present invention is described in detail next through the practical examples.

Practical Example 1

3.0 g N-isopropyl acrylamide, 0.158 g butylmethacrylate, 0.0288 g ethylene glycol dimethacrylate, and 0.009 g tert-butyl-peroxy-2-ethylhexanoate were dissolved in 3 mL of 1,4-dioxane, purged for 10 minutes with N_2 gas, poured between glass plates having a 0.05 to 0.5 mm spacer therebetween, and allowed to react for 12 hours at 30°C in an oven to obtain a gel membrane. This was washed for 2 days in each of methanol, water/methanol (1/1) and water to obtain a hydrogel of a copolymer having a 5 wt.% butylmethacrylate, 1 wt.% ethylene glycol dimethacrylate and 94 wt.% N-isopropyl acrylamide composition. This hydrogel membrane was inserted between two jacketed chamber cells, a phosphate buffer was placed in the respective chambers, after which nitroglycerin was placed in one chamber to obtain a suspension. Samples were taken chronologically from the other chamber and the nitroglycerin concentration was measured by HPLC. The change over time in the cumulative amount of permeated nitroglycerin when the temperature was changed in stages at 32°C and 22°C is shown in Fig. 1. Japanese white domestic rabbits (male, 14 weeks old, 2.4 to 2.5 kg) were immobilized in a supine position under pentobarbital anesthesia, their abdomens were clipped of fur with a barber's clipper and subsequently shaved carefully with a razor. The jacketed glass cell in which the nitroglycerin suspension was placed was stuck there by way of the above-mentioned hydrogel membrane. 1 to 3 mL of blood were collected over time from the aortocoronary artery in which a catheter was inserted, and the concentration of the nitroglycerin in the plasma was measured by HPLC or ECD gas chromatography. The concentration

profiles of the nitroglycerin in the plasma at 22°C after 6 hours and at 32°C after 6 hours are shown in Fig. 2.

Practical Example 2

3.0 g N-isopropylacrylamide, 0.2433 g butylmethacrylate, 0.0293 g ethylene glycol dimethacrylate, and 0.009 g tert-butyl-peroxy-2-ethylhexanoate were dissolved in 3 mL of 1,4-dioxane and polymerized, and the membrane was formed and washed as in Practical Example 2 to obtain a hydrogel membrane of a copolymer having a 7.5 wt.% butyl methacrylate, 1 wt.% ethylene glycol dimethacrylate and 91.5 /144 wt.% N-isopropyl acrylamide composition. The results upon evaluating it as in Practical Example 1 are shown in Figures 1 and 2.

Practical Examples 3 and 4

Upon performing the test as in Practical Example 1, except for using N-acryloyl piperidine (Practical Example 3) or N-acryloylmorpholine (Practical Example 4) in place of the N-isopropylacrylamide in Practical Example 1, it was confirmed that the resulting gel member had temperature-responsiveness in each example and on/off control of the drug was possible in either example.

4. Brief Description of the Drawings

Figure 1 shows the change over time in the cumulative amount of permeated nitroglycerin and Fig. 2 shows the change over time in the concentration of nitroglycerin in plasma.

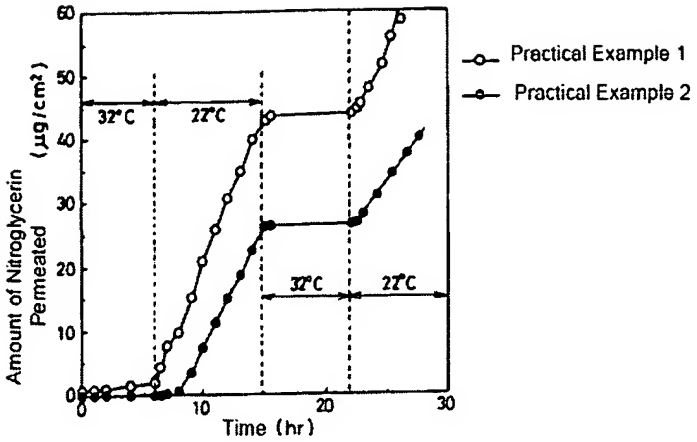


Figure 1

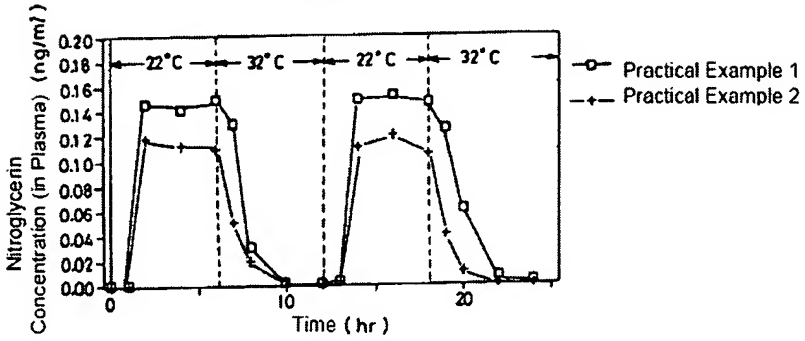


Figure 2